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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,140	09/08/2003	Yuanxiang Tao	001107.00388	8826

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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04/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,140	TAO ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7,10,11,13,16,17,19-22,24,25,34,62 and 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7,10,11,13,16,17,19-22,24,25,34,62 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *December 26, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed December 26, 2007.

Claims 6, 12, and 18 have been canceled. Claims 1, 7, 13, and 19 have been amended.

Claims 1, 4, 5, 7, 10, 11, 13, 16, 17, 19-22, 24, 25, 24, 34, 62, and 64 are pending in the instant application.

Claims 1, 4, 5, 7, 10, 11, 13, 16, 17, 19-22, 24, 25, 24, 34, 62, and 64 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed December 26, 2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed September 25, 2007, claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. **This rejection is moot** against claims 6, 12, and 18 in view of Applicant's Amendment to cancel these claims. **This rejection is withdrawn** against claims 1, 4, 5, 7, 10, 11, 13, 16, 17, 19-22, 24, 25, 24, 34, 62, and 64 in view of Applicant's Amendment filed December 26, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to spell out the term "PSD95".

In the previous Office Action mailed September 25, 2007, claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is moot** against claims 6, 12, and 18 in view of Applicant's Amendment to cancel these claims. **This rejection is withdrawn** against claims 1, 4, 5, 7, 10, 11, 13, 16, 17, 19-22, 24, 25, 24, 34, 62, and 64 in view of Applicant's Amendment and Remarks filed December 26, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to spell out the term "PSD95" and in view of Applicant's Remarks that adequate written description of a nucleic acid molecule which is well known in the art does not require a structural recitation either in the specification or in the claims. Further, the Examiner is withdrawing this rejection in view of Applicant's reference to Example 15 of the Written Description Training Guidelines. Specifically, the Examiner acknowledges that the claims are limited to antisense oligonucleotides which are complementary to mRNA encoding human PSD95 and which inhibit expression of human PSD95, where human PSD95 was known in the art at the time of

filing, being identified as GenBank Accession No. U83192.

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In the previous Office Action mailed September 25, 2007, claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical formulation comprising an isolated and purified antisense polynucleotide which is complementary to PSD95 mRNA and comprises SEQ ID NO:1, and a method for relieving acute or chronic pain, treating or preventing hyperalgesia, or reducing a threshold for anesthesia comprising the intrathecally administration of an antisense oligonucleotide which is complementary to mRNA encoding human PSD95, wherein the antisense inhibits the expression of PSD95, and the antisense comprises SEQ ID NO:1, does not reasonably provide enablement for any pharmaceutical formulation comprising an isolated and purified antisense polynucleotide which is complementary to PSD95 mRNA or a method for relieving acute or chronic pain, treating or preventing hyperalgesia, or reducing a threshold for anesthesia comprising any route of administration of any antisense oligonucleotide which is complementary to mRNA encoding human PSD95. **This rejection is moot** against claims 6, 12, and 18 in view of Applicant's Amendment to cancel these claims. **This rejection is maintained** against claims 1, 4, 5, 7, 10, 11, 13, 16, 17, 19-22, 24, 25, 24, 34, 62, and 64 for the reasons of record set forth in the previous Office Action mailed September 25, 2007.

Response to Arguments

In response to this rejection, Applicants argue that the proper standard for determining whether the present specification meets the enablement requirement is whether any experimentation which may be needed to practice the methods is undue or unreasonable. Applicants rely on *In re Wands*. Applicants contend that the Patent Office has not made a *prima facie* case that undue or unreasonable experimentation is needed to practice the claimed invention. Specifically, Applicants argue that the amino acid sequence of human PSD95 is virtually identical to the amino acid sequence of rat PSD95 and in view of this evidence, it is not scientifically reasonable to contend that the mRNA molecules encoding the human and the rat proteins are so vastly different that the specification's example using a rat antisense oligonucleotide is not probative of enablement of human antisense oligonucleotides.

Applicant's arguments and contentions have been fully considered, but are not found persuasive because the primary issue is not that the rat antisense oligonucleotide taught in the instant specification and in the prior art is not probative of enablement of a human antisense oligonucleotide. Instead, and as discussed in the previous Office Action mailed September 25, 2007, particularly at pages 9-16, the primary issue is that neither the specification nor the prior art teach any other effective antisense, rat, human, or otherwise, that functions in the methods as claimed. Absent this evidence, the quantity of experimentation in this area of art is extremely large as it requires the analysis and *de novo* determination of those antisense oligonucleotides which are complementary to mRNA encoding human PSD95 that, upon administration, are

effective in methods for relieving acute or chronic pain or treating or preventing hyperalgesia in a human subject. Also, as discussed in the previous Office Action mailed September 25, 2007, as neither the prior art nor the specification provide guidance as to the structure of other antisense oligonucleotides which are complementary to mRNA encoding human PSD95 that function in the methods as claimed, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Specifically, screening each possible antisense oligonucleotide which is complementary to mRNA encoding human PSD95 to determine its ability to relieve acute or chronic pain or treat or prevent hyperalgesia is unpredictably undertaking in itself, with each of the many intervening steps, not providing any guarantee of success. In this regard, the *Wands* factors have been weighed and favor undue experimentation.

Applicants next argue that Agrawal et al. (2000), as cited in the previous Office Action mailed September 25, 2007 provides guidance and speaks positively of the success of antisense therapy. Applicants point the Examiner to Agrawal et al. at page 809 and Figure 3.

This argument has been fully considered, but is not found persuasive because although Agrawal et al. may speak positively of the success of antisense therapy at page 80, paragraph 1 of Concluding Remarks, it should be also noted that in this same paragraph, Agrawal et al. disclose, “[A]s is always the case, caution must be exerted in experimental design and interpretation of antisense results until all the critical aspects of antisense oligonucleotides are explored beyond a reasonable doubt". Given this

caveat, it is the Examiner's position that the overall state of the art of antisense gene therapy is highly unpredictable as discussed and summarized in the review articles of Agrawal et al. (1996), Agrawal et al. (2000), and Tamm et al., made of record in the previous Office Action mailed September 25, 2007.

Applicants next argue that the evidence of record weighs heavily in favor of enablement. Applicants point the Examiner to nine references provided in Applicant's previous response filed January 18, 2007 that provided a sampling of numerous clinical trials using a variety of antisense oligonucleotides that had been carried out and reported at the time of Applicant's invention. Applicants contend that the Examiner dismissed these nine references and thus has not made a *prima facie* case that the claims are not enabled.

Applicant's arguments and contentions have been fully considered, but are not found persuasive because as discussed *supra*, it is the Examiner's position that the overall state of the art of antisense gene therapy is highly unpredictable as discussed and summarized in the review articles of Agrawal et al. (1996), Agrawal et al. (2000), and Tamm et al., made of record in the previous Office Action mailed September 25, 2007. Contrary to Applicant's assertions, the Examiner did fully consider the nine references that Applicants provided in their response filed January 18, 2007. However, these references were not found persuasive because the review articles of Agrawal et al. (1996), Agrawal et al. (2000), and Tamm et al., made of record in the previous Office Action mailed September 25, 2007, and the review articles of Jen et al. and Chirila et al. made of record in the previous Office Action mailed October 18, 2006, provide a more

accurate review of the overall state of the art of antisense therapy. More accurate than the sampling of numerous clinical trials using specific antisense oligonucleotides provided by Applicants in their nine references filed and made of record on January 18, 2007.

In summary, the specification provides only guidance regarding a single pharmaceutical antisense oligonucleotide that functions in the methods as claimed. The evidence of record shows that resolution of the various complications in regards to targeting a particular gene in an organism for gene therapy purposes is highly unpredictable. Therefore, the evidence of record weighs more in favor of nonenablement and supports that one of skill in the art would have been unable to practice the invention, over the scope claimed, without engaging in undue trial and error experimentation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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tcg
March 26, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635